

Amendments to the Claims

1. (Currently amended) A nucleic acid molecule comprising a P66^{shc} coding sequence incorporating at least one mutation as compared to the wild type sequence or the sequence as shown in SEQ ID NO: 1 Fig. 5 such that the protein encoded by the coding sequence has at least one serine residue absent or replaced by a different amino acid residue.
2. (Currently amended) A nucleic acid molecule according to claim 1 wherein the serine residue is selected from the group consisting of S17, S19, S20, S26, S28, S36, S38, S40, S41, S54, S60, S66, S80 and S102 ~~S120~~.
3. (Previously Presented) A nucleic acid molecule according to claim 1 wherein the serine residue is selected from the group consisting of S28, S36 and S54.
4. (Previously presented) A nucleic acid molecule according to claim 1 wherein the serine residue is S36 and is replaced by alanine (p66^{shc}S36A).
5. (Previously Presented) A polypeptide encoded by a nucleic acid molecule according to claim 1.
6. (Previously presented) A replicable vector comprising nucleic acid according to claim 1 operably linked to control sequences to direct its expression.
7. (Original) A host cell transformed with a vector according to claim 6.
8. (Original) A method of producing a modified p66^{shc} polypeptide comprising culturing a host cell according to claim 7 so that the p66^{shc} polypeptide is produced.

9. (Currently amended) A method of modulating resistance in cells to oxidative stress by affecting the p66^{shc} signal transduction pathway in a cell, said method comprising the step of contacting said cell with an agent capable of modulating p66~~shc~~^{shc} gene expression.
10. (Previously Presented) A method according to claim 9 wherein said agent is a nucleic acid molecule capable of hybridizing to nucleic acid encoding p66^{shc} thereby reducing or preventing said p66shc thereby reducing or preventing said p66^{shc} expression.
11. (Original) A method according to claim 9 wherein said agent is a vector comprising nucleic acid encoding p66^{shc}, said vector being capable of incorporating said nucleic acid into the genome of the cell so that the nucleic acid encoding p66shc is expressed in the cell.
12. (Currently amended) A method of increasing resistance in cells to oxidative stress comprising the step of disrupting the ~~pathway~~ p66^{shc} signaling pathway.
13. (Currently amended) A method according to claim 12 wherein said step of disrupting the p66^{shc} ~~effects~~ affects the susceptibility of p66^{shc} to phosphorylation.
14. (Previously Presented) A method according to claim 12 wherein said step of disrupting the p66^{shc} pathway causes a mutant p66^{shc} polypeptide to be expressed such that at least one serine residue present in the wild type p66^{shc} is absent or replaced by a different amino acid residue.
15. (Previously Presented) A method according to claim 14 wherein said serine residue is S36 and is replaced by alanine.
16. (Original) A method according to claim 14 wherein said mutant polypeptide cannot be serine phosphorylated.

17. (Currently amended) A method according to claim 12 wherein said disruption affects ~~effects~~ the ability of a serine/threonine kinase, p38 or MAPK to phosphorylate p66^{shc}.
18. (Previously presented) A method according to claim 12 wherein the step of disrupting the p66shc signaling pathway includes contacting the cell with an antibody binding domain capable of specifically binding to the p66^{shc} polypeptide such that its function is disrupted or prevented.
19. (Previously presented) A method according to claim 12 wherein said step of disrupting the p66^{shc} signaling pathway includes disrupting the p66^{shc} gene expression.
20. (Original) A method according to claim 19 wherein disruption of the p66^{shc} gene expression includes contacting the cell with a substance capable of interfering with the expression of nucleic acid encoding the p66^{shc} polypeptide so as to reduce or prevent its production.
21. (Previously presented) A method according to claim 20 wherein the substance is an antisense oligonucleotide capable of hybridizing to the nucleic acid encoding the p66shc polypeptide.
22. (Previously presented) A method for increasing cellular resistance to oxidative stress comprising administration of an effective amount of an agent which disrupts p66^{shc} or a step in the p66^{shc} signaling pathway in a pharmaceutically acceptable carrier.
23. (Previously presented) A method as claimed in claim 22 wherein said agent is an antisense oligonucleotide capable of specifically hybridizing to p66^{shc} nucleic acid.
24. (Previously presented) A method according to claim 23 wherein said antisense oligonucleotide is RNA.

25. (Previously Presented) A method according to claim 23 wherein the p66^{shc} nucleic acid sequence is shown in Fig. 5.
26. (Previously Presented) A method according to claim 22, wherein said agent is an antibody binding domain capable of specifically binding to a p66^{shc} polypeptide or fragment thereof.
27. (Previously Presented) A method as claimed in claim 22 wherein said agent is administered for the treatment of diseases selected from the group consisting of lung emphysema, myocardial infarction, stroke, premature aging, cell senescence, Parkinson's, Alzheimer, cancers and diabetes.
28. (Previously presented) A method of increasing resistance to tumor formation in a tissue comprising the step of increasing the expression of p66^{shc} in said tissue.
29. (Original) A method according to claim 28 wherein the step of increasing the expression of p66^{shc} includes contacting the tissue with an agent capable of increasing expression of p66^{shc} gene.
30. (Original) A method according to claim 29 wherein said agent is a transcription factor.
31. (Original) A method according to claim 29 wherein said agent is a vector comprising nucleic acid encoding p66^{shc} polypeptide said vector being capable incorporating said nucleic acid into the genome the cells of the tissue.
32. (Currently amended) A method of screening for compounds capable of modulating resistance in cells to oxidative stress by modulating the a p66^{shc} signaling pathway comprising contacting a candidate compound with a p66^{shc} expression system; determining the amount of a compound of the signaling pathway; and comparing said amount of the component with the

amount of the component in the absence of said candidate compound.

33. (Original) A method according to claim 32 further comprising the step of preparing a pharmaceutical composition comprising the candidate compound capable of modulating a p66^{shc} pathway and a pharmaceutical acceptable carrier.

34. (Previously presented) A method according to claim 32 wherein said step of determining the amount of a compound of the signaling pathway is an enzyme activity assay.

35. (Previously Presented) A method according claim 32 wherein said candidate compounds include nucleic acid sequences, antibody binding domains, and protein nucleic acids.

36. (Original) A method of reducing intracellular levels of reactive oxygen species (ROS) in a cell, said method comprising the step of contacting said cell with an agent capable of inhibiting the expression or activity of p66^{shc} polypeptide.

37. (Previously presented) A method according to claim 36 wherein said agent is a nucleic acid molecule capable of specifically hybridizing with nucleic acid with the cell which codes for the p66^{shc} polypeptide such that expression the p66^{shc} polypeptide is reduced or prevented.

38. (Original) A method according to claim 36 wherein the agent is an antibody binding domain capable of specifically binding to the p66^{shc} polypeptide such that its functions are inhibited or prevented.

39. (Canceled)

40. (Canceled)

41. (Canceled)

42. (Previously presented) A method of determining the presence or absence of a p66^{shc} nucleic acid or a mutant, variant derivative or allele thereof in a biological sample, comprising the step of contacting said sample with a nucleic acid molecule capable of hybridizing specifically with said p66^{shc} nucleic acid or a mutant, variant derivative or allele thereof and determining whether or not hybridization has taken place.
43. (Currently amended) A method of determining the presence or absence of a p66^{shc} polypeptide or a mutant, variant derivative or allele thereof in a biological sample, comprising the step of contacting said sample with an antibody binding domain capable of binding ~~hybridizing specifically with said p66^{shc} nucleic acid~~ or a mutant, variant derivative ~~or allele~~ thereof and determining whether or not ~~hybridization~~ binding has taken place.
44. (Original) An expression system comprising a nucleic acid vector having a p66^{shc} coding sequence or fragment thereof inserted therein.
45. (New) A method according to claim 10 wherein said agent is a vector comprising nucleic acid encoding p66^{shc}, which when expressed in a cell results in production of p66^{shc}.
46. (New) A method according to claim 10, wherein the nucleic acid molecule is an antisense oligonucleotide capable of hybridizing to the nucleic acid encoding the p66^{shc} polypeptide.
47. (New) The method of claim 46, wherein said antisense oligonucleotide is RNA.
48. (New) A method according to claim 9, wherein said agent acts to increase resistance to oxidative stress in cells by disruption of the p66^{shc} signaling pathway.

49. (New) A method according to claim 9, wherein said agent acts to increase cellular resistance to oxidative stress by disruption of p66^{shc} or by disruption of a step in the p66^{shc} signaling pathway.
50. (New) A method according to claim 49, wherein said agent is an antisense oligonucleotide which specifically hybridizes with a nucleic acid encoding p66^{shc}.
51. (New) A method according to claim 50, wherein said antisense oligonucleotide is RNA.
52. (New) A method according to claim 48, wherein said agent is administered for the treatment of a disease selected from the group consisting of arteriosclerosis, ischemic heart disease, lung emphysema, myocardial infraction, stroke, premature aging, cell senescence, Parkinson's, Alzheimer's, cancer and diabetes.